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Response to the editorial by Dr Geraghty. In press Journal of Health Psychology

PD White¹, T Chalder², M Sharpe³, BJ Angus⁴, HL Baber¹, J Bavinton⁵, M Burgess⁶, LV Clark¹, DL Cox⁷, JC DeCesare¹, KA Goldsmith⁸, AL Johnson⁹, P McCrone¹⁰, G Murphy¹¹, M Murphy⁵, H O'Dowd¹², L Potts⁸, R Walwyn⁸, D Wilks¹³

¹ Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine, Queen Mary University of London, London, UK

² Academic Department of Psychological Medicine, King's College London, London, UK

³ Psychological Medicine Research, Department of Psychiatry, University of Oxford, Oxford, UK

⁴ Nuffield Department of Medicine, University of Oxford, The John Radcliffe Hospital, Oxford, UK

⁵ Barts and the London NHS Trust, London, UK

⁶ South London and Maudsley NHS Foundation Trust, London, UK

⁷ Faculty of Health and Well Being, University of Cumbria, Lancaster, UK

⁸ Biostatistics & Health Informatics Department, Division of Psychology and Systems Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London. UK

⁹

Medical Research Council Clinical Trials Unit, London, UK

¹⁰ Centre for the Economics of Mental Health Service and Population, King's College London, London, UK

¹¹ Royal Free Hospital NHS Trust, London, UK

¹² Frenchay Hospital NHS Trust, Bristol, UK

¹³ Western General Hospital, Edinburgh, UK

Correspondence to Prof Peter White, Academic Psychological Medicine, St Bartholomew's Hospital, London, EC1A 7BE, UK p.d.white@qmul.ac.uk

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Abstract

This paper is written in response to the linked editorial by Dr Geraghty about the PACE trial, which we led, implemented, and published. The PACE trial compared four treatments for people diagnosed with chronic fatigue syndrome (CFS). All participants in the trial received specialist medical care (SMC). The trial found that adding cognitive behaviour therapy (CBT) or graded exercise therapy (GET) to SMC was as safe as, and more effective than, adding adaptive pacing therapy (APT) or SMC alone. Dr Geraghty has challenged these findings. In this paper, we suggest that Dr Geraghty's views are based on misunderstandings and misrepresentations of the PACE trial; these are corrected.

The PACE trial compared four treatments for people diagnosed with chronic fatigue syndrome (CFS) (White et al., 2011). A recent editorial about this trial (Geraghty, 2016) contains a number of inaccuracies which we now correct.

1. Dr Geraghty states that “...there are accepted scientific procedures and standards that appear to have been neglected, or bypassed, by the PACE-Trial team”, although he has not said which procedures and standards we neglected or bypassed. The trial was extensively peer reviewed by the Medical Research Council, which funded it. It followed the CONSORT guidance on how to report and conduct a high quality trial (<http://www.consort-statement.org/>). A Research Ethics Committee gave ethical approval, and it was overseen throughout by the independent Trial Steering Committee and Data Monitoring and Ethics Committee; patient members sat on the Trial Management and Steering Committees. The protocol was published some three years before the analysis began, and four years before the first outcome paper was published (White et al., 2007). The papers reporting the trial findings were peer reviewed before their publication in high impact journals, such as The Lancet (White et al., 2011). So far, we have published 16 papers from the trial (<http://www.wolfson.qmul.ac.uk/current-projects/pace-trial>), as well as contributing data to an individual patient data Cochrane Collaboration review, which has been submitted for publication.

2. We reject the accusation that our “actions have arguably caused distress to patients,” for which Dr Geraghty offers no evidence. People with CFS and/or ME want treatments that help them to improve (Action for ME, 2011). In this ME charity member survey of NHS services, 85% of those surveyed wanted the charity to campaign to save these services and 92% wanted more such services; 46% had received CBT and 65% thought that CBT should be made available; 31% had received GET, and 48% thought it should be made

available (Action for ME, 2011). The PACE trial simply confirmed what previous smaller trials had already found (Edmonds et al., 2004; Price et al., 2008): that patients are more likely to get better with either CBT or GET than with other treatments or usual care.

3. We reject the suggestion that the fact that we use these therapies for our patients and have tested them in previous trials is “a major source of investigator bias”. Clinical research often arises from questions thrown up by clinical practice. The clinicians amongst us have dedicated our careers to care for thousands of patients with CFS/ME and we always want the best for them. We are therefore obliged to conduct trials to test the effectiveness and cost-effectiveness of treatments that we use. If Dr Geraghty’s proposal, that trials should only be conducted by investigators with no previous experience of an illness and its treatments, was followed, it would prevent any clinician or researcher from attempting to replicate or refute the results of their earlier trials. Whilst steps should always be taken to minimise bias, as we did, this suggestion is not sensible.

4. In our long-term follow up paper we reported that the benefits of CBT and GET were maintained some two years after treatment (Sharpe et al., 2015). Dr Geraghty suggests that “The trial authors have since [the paper was published] argued that the SMC and APT groups [who improved over the follow up period], probably went to get CBT or GET privately after the end of the formal trial.” The reality is that we clearly reported within the paper the numbers of participants who went on to receive the additional therapies (most commonly CBT and GET), which were offered by trial NHS therapists to all participants who needed and wanted further help.

5. Regarding our paper on recovery Dr Geraghty stated that we defined it partially on the basis of “a patient reporting feeling ‘better’ or ‘much better’” when in reality ratings of overall health as “much better “ or “very much better” counted towards being considered recovered on this measure.

6. Dr Geraghty is also incorrect in his comments about the repeated use of the Freedom of Information Act (FOIA) to obtain trial information – “the PACE authors ... refused to release data partly on the grounds that they viewed requesters as vexatious patients ...”. Of the 46 FOIA requests that Queen Mary University of London have received, only two requests (not the requesters) were considered vexatious by the University; this view was confirmed by the Information Commissioner on appeal (Information Commissioners Office 2016a & b).

7. We have repeatedly addressed the criticisms made in the editorial of the methods and analyses used in the PACE trial. These can be found in blogs (Wessely, 2015, White et al., 2016a), journal correspondence, and as answers to frequently asked questions on the PACE trial website (<http://www.wolfson.qmul.ac.uk/current-projects/pace-trial#patients>).

8. In the editorial Dr Geraghty makes two criticisms, which we have not previously addressed. In the first one he states that “the effectiveness of cognitive behaviour therapy (CBT) and graded exercise therapy (GET), , fell by two thirds” in a reanalysis of some of the trial data, and concludes that these “have left us with two versions of ‘truth’ concerning the trial’s findings – the published analysis versus the recent analysis.” This is incorrect. Effectiveness was measured by comparing the mean scores for each of the two primary outcomes between treatment groups; the effect sizes varied between 0.5 and 0.8 (moderate effect sizes), depending on the different comparisons (White et al., 2011). In his editorial, Dr Geraghty has compared two different things: One is a

secondary post hoc analysis from the main paper, in which we reported the proportions of participants who improved by a clinically useful amount in both the primary outcomes (an improvement of 8 or more points for physical function and 2 points for fatigue), which equated to 61% for CBT and 59% for GET (White et al., 2011). The other is our reanalysis of some of the trial data comparing the proportions of participants who met a composite threshold for improvement (either improving by 50% on the primary outcomes or meeting a threshold for improvement) (Goldsmith et al., 2016). Using this composite outcome, 21% improved with GET and 20% with CBT; significantly more than with APT (9%) or SMC alone (10%) (Goldsmith et al., 2016). Dr Geraghty suggests that the effectiveness fell from 61% by one analysis method to 20% when using another method. It is no surprise that fewer participants are regarded as improved if more stringent criteria are applied. Since this has nothing to do with efficacy, it made no difference to our interpretation that “CBT and GET can safely be added to SMC to moderately improve outcomes for chronic fatigue syndrome, but APT is not an effective addition.” (White et al., 2011). The later analysis was described in our original protocol and then abandoned for the definitive analysis plan after statistical advice (Walwyn et al., 2013). This was because we accepted that using composite outcomes was complex, difficult to interpret, and incongruent with expert views (Senn and Julious, 2009). We changed this analysis with oversight committee approvals, and before outcome data were examined (White et al., 2011; Walwyn et al., 2013).

9. The second criticism concerned our secondary analysis paper about recovery (White et al., 2013). Dr Geraghty states that “... some trial participants had reached the level required to be classified as improved or recovered at trial entry.” This is incorrect; 3/640 (<1%) of participants had scores within the normal population ranges for both fatigue and physical function at trial entry, which was only *one* of the criteria necessary to be considered as recovered. To meet the criteria for recovery, a participant *also* had to have

met additional criteria: no longer be considered a case of CFS (using the trial definition of CFS), and rated their overall health as “much” or “very much” better compared to trial entry. *No* participants met the full criteria for recovery at trial entry.

10. Regarding comments on the release of trial data, we wish to clarify that one of the main reason for our refusal to provide individual patient data to members of the public (following a Freedom of Information Act request) was that we do not have the consent of our participants to make their data publicly available. We were also concerned that patients might be personally identified by releasing the data. We support sharing data for the benefit of medical research and ultimately of patients (White et al., 2016b), as long as it is subject to certain guarantees – principally concerning confidentiality and an agreement not to attempt to identify participants. This is an ethical position, respecting patients’ rights, as we are required to do by research governance and the data protection law, and has been repeatedly supported by the Information Commissioner and Information Tribunal on all but one occasion.

We stand firmly by the findings of the PACE trial, which, along with other studies, provide patients, healthcare professionals, and commissioners with the best evidence that both CBT and GET are safe and effective treatments for this chronic and disabling illness. Others share this view (National Institute for Health and Clinical Excellence 2011; The Lancet 2011; NHS Choices 2011; The Lancet 2015). These findings are good news for patients who, in our experience, just want to get better. Of course, we need further trials, not only of CBT and GET, but also other treatments. To this end, we hope that editorials such as that by Dr Geraghty do not discourage others from doing such research. .

Declaration of conflicting Interests

All authors were members of the PACE trial team. Affiliations are almost all given as at the time of the PACE trial main paper. PDW is a member of the Independent Medical Experts Group, which advises the Ministry of Defence regarding the Armed Forces Compensation Scheme. He has done unpaid consultancy for the Department for Work and Pensions, and does paid consultancy for a re-insurance company. MS has received royalties from several publishers of academic books. TC and MB have received royalties from a book. JB is a director of the company Vitality360. Note: most author affiliations are current, but some pertain to the time when the PACE trial main paper was published in 2011.

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